ORIGINAL ARTICLE

Neutrophil-Lymphocyte Ratio and Ischemia-Modified Albumin in Predicting Carbon Monoxide-Delayed Neurological Sequelae

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Abstract

Background: Carbon monoxide (CO) poisoning is a widespread cause of morbidity and mortality, with delayed neurological Sequelae (DNS) among the most severe consequences of this silent killer.
Objectives: To study the relationship between neutrophil-lymphocyte ratio (NLR), ischemia-modified albumin (IMA), and severity of acute CO poisoning as well as their role in predicting delayed neurological manifestations.
Patients and Methods: Sixty acutely CO-intoxicated patients were admitted to Alexandria Poison Center, Egypt. NLR and IMA were assessed. Six months after discharge, all patients were subjected to neuropsychometric testing using Mini-Mental Status Examination (MMSE). Brain magnetic resonance imaging (MRI) was conducted on cognitively impaired patients.
Results: NLR was abnormally high in most patients and the mean serum level of IMA was significantly elevated in acutely CO-intoxicated patients compared to the control group (P<0.001). NLR and IMA were significantly related to neurological manifestations and other laboratory parameters. Patients were subdivided into DNS group (n = 16) and non-DNS group (n = 44), according to MMSE and brain MRI done after six months, with significant elevation of NLR and IMA in DNS group (p<0.001). The accuracy of DNS prediction parameters was measured using the area under the receiver operating characteristics curve. Excellent accuracy was detected for IMA and NLR.
Conclusion: The studied markers of NLR and IMA assessed on admission could be employed as useful biomarkers for correlating with acute CO poisoning severity and predicting the outcome including the possibility of development of DNS.

Keywords: Carbon monoxide poisoning, Neutrophil-lymphocyte ratio, Ischemia- modified albumin

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INTRODUCTION

Carbon monoxide poisoning is a common cause of injury and death in all countries. In 2020, the cumulative incidence and mortality of CO poisoning were appraised to be 137 cases and 4.6 deaths per million, respectively [1, 2]. In Egypt, CO poisoning represented the 6th most frequent toxic exposure in 2004 [3].

This "silent killer," as sometimes termed, is mainly produced by incomplete combustion of organic compounds. It is odorless, colorless, tasteless, and lighter than air [4].

There are several metabolic changes in the pathophysiology of acute CO poisoning due to tissue hypoxia with the formation of carboxyhemoglobin (COHb). Hence, the oxygen-hemoglobin dissociation curve is shifted to the left, hindering oxygen dissociation in the low-oxygen region, and potentiating tissue hypoxia causing deficient oxygenation at the tissue level [5].

CO inhibits mitochondrial respiration by binding to the ferrous heme a3 in the active site of cytochrome oxidase (COX), shutting down oxidative phosphorylation [6]. Most CO poisoned patients experience both hypoxia and ischemia. White blood cells (WBCs) adhere to damaged endothelial cells during recovery from CO exposure, releasing enzymes and resulting in oxidative stress. Moreover, nitric oxide (NO) displaced from platelets surface hemoproteins by CO can react with superoxide forming peroxynitrite, further impairing mitochondrial function, releasing reactive oxygen species (ROS), causing more lipid peroxidation and apoptosis leading to neurological and cardiac complications [7, 8].

A serious neurological complication is the development of delayed neurological Sequelae (DNS) [9]. It is defined as any new neurological, cognitive, or affective disorder that develops after an asymptomatic period following acute CO poisoning [10, 11].

Activated platelets can encourage neutrophils to degranulate, releasing the inflammatory mediator myeloperoxidase (MPO). MPO amplifies the inflammatory effects by triggering more neutrophil activation, adhesion, and degranulation [12].Neutrophil-lymphocyte ratio (NLR) is

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a combination of two independent parameters; neutrophils as a marker of ongoing nonspecific inflammation and lymphocytes as a marker of the regulatory pathway [13]. Being cheap, easy, noninvasive, and broadly available made the combination of these two markers (NLR) a powerful simple marker of systemic inflammation [14]. Recently, it gained an increased concern due to its role, as an independent prognostic factor, in many conditions such as local or systemic infection and some other inflammatory diseases [15].

Human serum albumin converts to ischemia-modified albumin (IMA) when the N- terminus of albumin is altered because of oxidative stress or ischemia. IMA is a nonspecific marker of tissue ischemia and oxidative stress induced by ischemia/reperfusion [16]. Moreover, IMA has mostly been studied, to date, in relation to different cardiac and cerebrovascular diseases associated with ischemia/ reperfusion [17].

Due to combined mechanisms of inflammation, oxidative stress, and ischemia in CO poisoning [7, 8, 12], NLR and IMA could be promising in the early detection of patients at risk of CO-related DNS development. After managing the acute manifestations of CO poisoning, the apparently healthy patients are discharged from poison centers. However, delayed neurological manifestations could appear later and unfortunately, these symptoms may be misdiagnosed and uncorrelated with previous CO poisoning. Therefore, this work aimed to study the relationship between NLR and IMA and severity of acute CO poisoning, and their role in predicting delayed neurological manifestations.

METHODS

This research was conducted on 60 patients with acute carbon monoxide poisoning admitted to Alexandria Poison Center, Egypt, following an approval from the medical research ethics committee of Faculty of Medicine, Alexandria University. (IRB Number: 00012089, FWA Number: 00018699, Approval serial number: 0201435). A written informed consent was obtained from patients or their guardians. Diagnosis of CO poisoning was based on history of exposure, clinical signs, and symptoms (as alteration in consciousness level, syncope, seizures, shortness of breath, chest pain, and palpitation) and was aided by measuring COHb blood level on admission using CO-oximeter incorporated in Siemens RAPID Point 500 Blood Gas Analyzer with analytical measurement range of 0.0 ± 200.0 % [18].

2.1 Exclusion Criteria:

It is critical to mention that patients with a history of pulmonary or coronary artery disease, peripheral arterial disease, acute mesenteric ischemia, acute ischemic cerebrovascular disease, and heart or liver failure or albumin levels of <3.5 g/dl and >5.5 g/dl were excluded from the study.

All the patients were subjected to:

- Full medical and toxicological history including (source, duration, and place of exposure to CO, number of exposed persons, delay time before arrival to emergency room (ER), symptoms of CO poisoning and pre presentation treatment.
- Thorough medical examination and assessment of level of consciousness using Glasgow Coma Scale (GCS), blood samples were obtained, and brain CT scan was done on arrival to the ER or during early hospitalization.
- Laboratory analysis was done for (ABG, COHb, CBC, CK-MB, troponin, and serum albumin).
- Neutrophil-lymphocyte ratio (NLR) was calculated by dividing neutrophil count by lymphocyte count [19].
- The estimation of Ischemia Modified Albumin: On admission, a venous blood sample was withdrawn from 60 patients and 30 healthy volunteer subjects, as a control group matched for age and sex with the studied patients to determine a cut off value as there is no standardized cut off value for IMA [20].
- After proper training to one of the research team, a neuropsychometric testing using Mini Mental Status Examination (MMSE) was done to all patients 6 months after discharge to assess cognitive function including (orientation, attention, memory, language, and visual spatial skills) [21].
- MRI was done to cognitively impaired patients. Follow-up was conducted for patients to detect the onset of DNS especially for those with neuropsychometric test abnormalities (using MMSE) or abnormal brain MRI findings or both.

2.2 Statistical Analysis

The obtained data were analyzed using the IBM SPSS software package version 20.0 (Armonk, NY: IBM Corp). Qualitative data were described using numbers and percentages. The Kolmogorov-Smirnov test was used to verify the normality of distribution. Quantitative data were described using range, mean, standard deviation, and median. Significance of the obtained results was judged at the 5% level.

The used tests were Chi-square test, Fisher's Exact or Monte Carlo correction, Student t-test, Mann Whitney test, Receiver operating characteristic curve (ROC), and Regression.

RESULTS

Out of sixty patients with acute CO intoxication in this study, 51.7% were females, while 48.3% were males, mostly from urban areas. The mean age was 32.03 ± 15.55 years and the mean exposure duration was 2.52 ± 5.09 h with 3.51 ± 4.94h until presented in APC.

Most patients (85%) were fully conscious on admission with GCS ranged from 9 to15, whereas one third of the patients presented with a dilated reactive pupil. Headache and drowsiness were the main presenting symptoms among >50% of the patients. Patients also suffered from sinus tachycardia (91.7), hypotension (76.7%), dyspnea (48.3%), chest pain (23%), nausea, vomiting (66%), and diarrhea (21.7%).

Metabolic acidosis was recorded in 91.7%, 25% were hypoxic, 31.7% needed hyperbaric oxygen (HBO), and 5% required mechanical ventilation. 70% showed elevated troponin (0.52±0.73 µg/ml). COHb was abnormally high in most patients (96.7 %) with a mean value of 25. 62 ± 10.32%, where a significant relation was recorded between COHb and GCS; $p = 0.047$ as well as systolic, diastolic blood pressure (SBP, DBP) ; $p< 0.001$, < 0.002, respectively.

Leukocytosis was detected in 17% of patients, with a mean WBC value of 11006.67 ± 3853.1, whereas 71.7% showed neutrophilia.

The serum marker, NLR was abnormally high in 70% of patients and showed a mean value of 6.09 ±5.03 that related significantly to GCS; p< 0.010, SBP; p< 0.006, DBP; p< 0.002, COHb; p< 0.001,WBCs; p = 0.010, troponin; p< 0.001 and need for HBO; p< 0.001.

IMA measured on admission was significantly elevated in CO-intoxicated patients compared with the control group (86.63 ± 70.76 µg /ml and 34.70±5.70 µg/ml respectively) (p< 0.001). IMA related significantly to GCS; p= 0.003, dyspnea; p= 0.027, SBP; p= 0.001, DBP p< 0.008, diarrhea; p= 0.007, (SaO2; p= 0.031, WBC; p= 0.042, troponin level; p< 0.001. Moreover, IMA was significantly associated with COHb (p< 0.001) and NLR (p< 0.001). Brain CT revealed abnormal findings in 40% of patients, 45.8% showed brain edema, whereas 54.2% showed areas of white matter hypodensities in 54.2%. Moreover, this study revealed a positive relation between laboratory and radiological investigations, where COHb, NLR and IMA related significantly to abnormal CT brain findings (p< 0.001).

The mean length of hospital stay was 2.87 ± 2.09 days that related significantly to COHb level, IMA and NLR among patients under study; (p< 0.001).

Six months after discharge, neurological assessment of patients was conducted to detect DNS using MMSE and brain MRI. Patients in this study were divided into the DNS group (26.7%) and the non-DNS group (73.3%). The DNS group showed cognitive impairment evidenced by lower MMSE scores than non-DNS group. Cognitive impairment was mild in 87.5% and severe in 12.5% of patients. More than a third (37.5%) of cognitively-impaired patients showed abnormal hyper-intense signals in white matter in brain MRI.

The starting age of the patients in DNS group in this study was 18 years old, up to 60 years old, with insignificant differences between DNS and non-DNS groups. Those who developed DNS were exposed to CO gas for a significantly longer mean duration than non-DNS group (6.66 ± 8.72 h and 1.02 ± 0.58 h, respectively) (P≤ 0.001).

On admission, the mean GCS of DNS group (12.81 ± 2.88) was significantly lower than that of non-DNS group (14.70 ± 1.37); p< 0.001. Blood pressure of DNS patients (SBP; 91.25 ± 3.42, DBP; 60.0 ± 0.0) was significantly lower than that of non-DNS group (SBP; 97.05 ± 4.62, DBP; 64.15 ± 4.99), p< 0.001.

Laboratory findings, including ABG, COHb, and troponin, showed statistically significant differences between DNS and non-DNS groups, as shown in Figure (1).

Patients in DNS group had significant neutrophilia and lymphopenia compared to non-DNS group (p=0.023, p=0.031). NLR and the novel biomarker IMA were significantly higher in DNS group than in non-DNS group (p< 0.001 each), as shown in Figure (2).

Abnormal findings in brain CT were significantly more frequent among DNS patients, additionally, they required more HBO than non-DNS group, with significantly longer duration of hospital stay (p< 0.001 each).

Univariate logistic regression analysis was performed to compare the predictive power of factors influencing DNS development. It was identified that different parameters were highly significant for predicting DNS development, including exposure duration, GCS, SBP, DBP, CT brain, HCO_3, SaO_2, IMA, NLR, and need for HBO (Table 1).

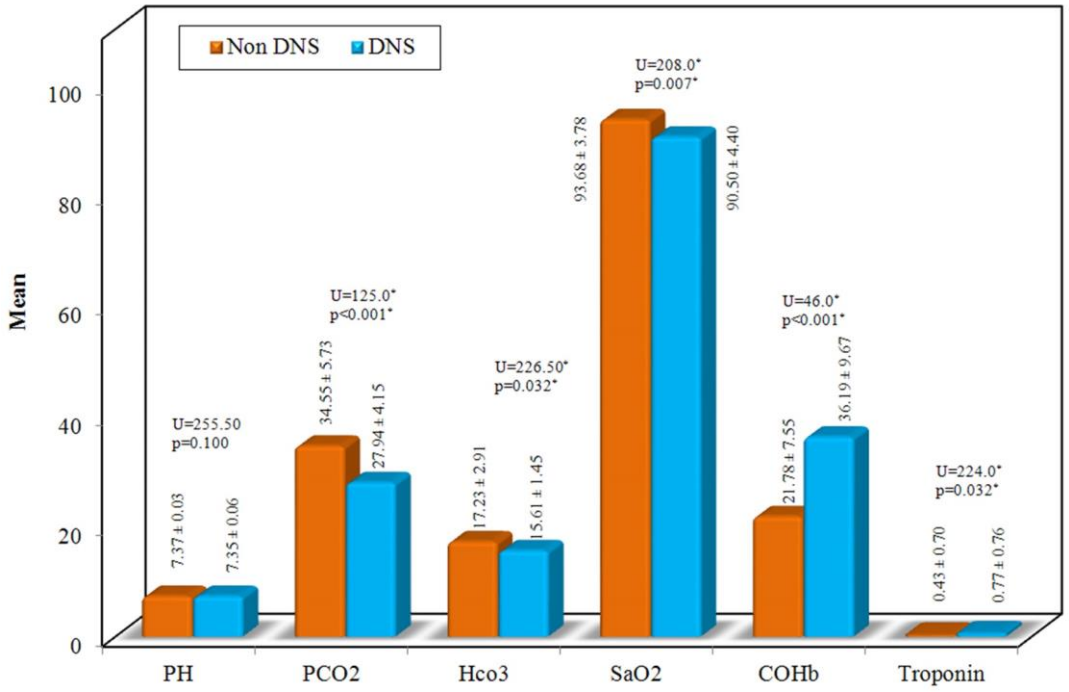

Figure 1. Relationship between delayed neurological Sequelae (DNS) and laboratory investigations (ABG, COHb and troponin) among CO-intoxicated patients (n = 60).

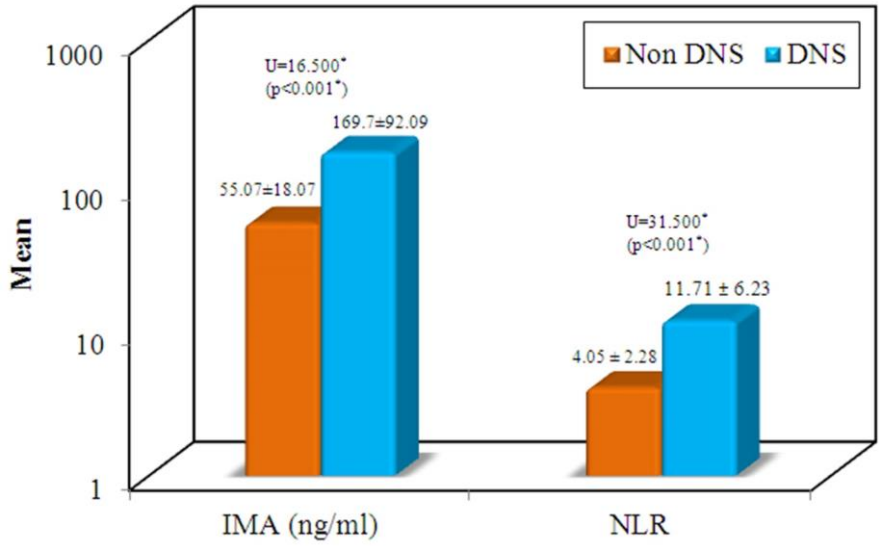

Figure 2. Relationship between delayed neurological Sequelae (DNS) and serum markers (NLR and IMA) among CO-intoxicated patients (n = 60).

Table 1. Univariate and Multivariate Logistic Regression Analysis for parameters affecting delayed neurological Sequelae (DNS) among CO-intoxicated patients (n = 60)

	Univariate		#Multivariate	
	p	OR (95%C.I)	p	OR (95%C.I)
Time passed since exposure (Hours)	0.004*	2.205 (1.293 – 3.760)	-	-
Duration of exposure (Hours)	0.001*	10.811(2.634–44.370)	-	-
Systolic blood pressure	0.001*	0.755 (0.642 – 0.887)	-	-
Diastolic blood pressure	0.012*	0.763 (0.618 – 0.942)	-	-
CT brain findings	0.997	–		
pH	0.329	0.001 (0.000 – 1687.444)		
PCO_2	0.001*	0.778 (0.674 – 0.897)	-	-
SaO_2	0.012*	0.837 (0.728 – 0.962)	-	-
HCO_3	0.047*	0.617 (0.383 – 0.994)	-	-
Hyperbaric	<0.001*	150.0(15.493-1452.25)	-	-
GCS	0.007*	0.663 (0.493 – 0.893)	1.000	0.932(0.001-0.01)
COHb	<0.001*	1.464 (1.183 – 1.811)	0.152	1.943(0.783-4.819)
IMA	0.003*	1.088 (1.030 – 1.150)	0.170	1.292(0.896-1.863)
NLR	0.001*	2.956 (1.529 – 5.715)	0.186	4.104(0.507-33.208)

OR: Odd`s ratio
C.I: Confidence interval LL: Lower limit UL: Upper Limit
#: All variables with p<0.05 was included in the multivariate
*: Statistically significant at $p \leq 0.05$

The accuracy of DNS prediction parameters was measured using the area under the receiver operating characteristics (ROC) curve. Excellent accuracy was detected for IMA, NLR, COHb, HBO, and CT brain with AUC (0.977, 0.955, 0.935, 0.923 and 0.909, respectively, while GCS had good accuracy with AUC =0.691. (Table 2, figure 3)

Regarding sensitivity and specificity of the biomarkers IMA and NLR, IMA had a sensitivity of 87.5% (could detect 87.5% of DNS-complicated patients) and a specificity of 100% (could detect 100% of non-DNS-complicated cases), at a cut-off value of >95 µg/ml. For NLR, it had a sensitivity of 93.75% and a specificity of 84.09, at a cut-off value of 5.67.

DISCUSSION

CO poisoning is a major clinical problem that results in significant morbidity and mortality all around the world. It is considered a predictable and preventable health-related condition [22].

Table 2. Validity (AUC, sensitivity, specificity) for NLR, IMA, COHB, GCS, CT brain to predict delayed neurological Sequelae (DNS) among CO-intoxicated patients (n = 60)

	AUC	p	95% C.I	Cut off#	Sensitivity	Specificity	PPV	NPV
NLR	0.955	<0.001*	0.903 – 1.000	>5.67	93.75	84.09	68.2	97.4
IMA	0.977	<0.001*	0.940 – 1.013	>95	87.50	100.0	100.0	95.7
COHB	0.935	<0.001*	0.876 – 0.993	>28	100.00	81.82	66.7	100.0
GCS	0.691	0.025*	0.523 – 0.860	≤13	43.75	95.45	77.8	82.4
CT brain	0.909	<0.001*	0.836 – 0.982	+ve	100.0	81.82	66.7	100.0
Hyperbaric	0.923	<0.001*	0.838 – 1.000	+ve	93.8	90.9	78.9	97.6

AUC: Area Under a Curve p value: Probability value
CI: Confidence Intervals
NPV: Negative predictive value PPV: Positive predictive value
*: Statistically significant at $p \leq 0.05$
#Cut off was chosen according to Youden index

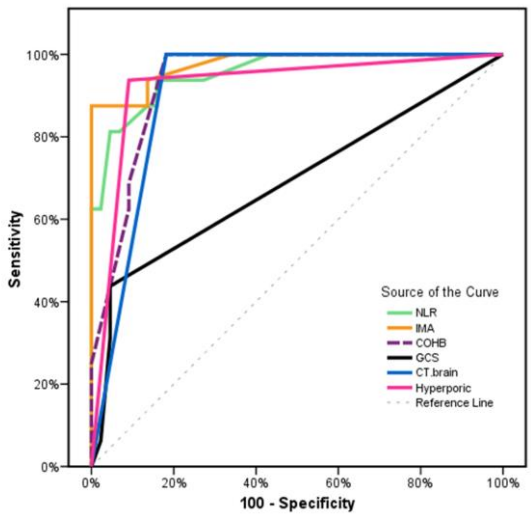

Figure 3. ROC curve for NLR, IMA, COHB, GCS, and CT brain to predict delayed neurological Sequelae (DNS) among CO-intoxicated patients (n = 60).

CO intoxication in this study included all age groups, with females being slightly affected more than males as most cases presented as a whole family. They mostly inhabit urban areas because of the widespread use of gas heaters. These findings agrees with that of Tahouri et al. (2017) [23].

Gastrointestinal manifestations were recorded in about two third of the patients, which commonly cause a misdiagnosis of acute CO poisoning as food poisoning; thus, a high level of suspicion is necessary to reach a CO intoxication diagnosis [24]. Most patients in this study presented with hypotension, with more than half of the cases suffering from headache and drowsiness, reflecting the effect of hypoxia on the most sensitive organs (heart and CNS) [25]. These results agree with those of Fawzi et al. (2011) [26], who reported hypotension and tachycardia in most cases [26]. Moreover, Abdel Aziz et al. (2021) [27] stated that headache, syncope, and vomiting were the most common presenting symptoms.

Brain edema and hypodensities in white matter were recorded in CT brain among 40% of patients in this study. This can be attributed to hypoxia, reduced cellular oxygen metabolism in the acute stage, and lipid peroxidation leading to oxidative injury, excitotoxicity, and later apoptosis; all of these may cause white matter damage [28]. Moreover, severe cases of CO poisoning may result in cytotoxic edema or swelling of brain cells [29]. These results agree with those of Lin et al. (2009) [30]. The effect of CO on white matter shown in CT brain of patients in this study could indicate that white matter is more prone to ischemia during early stages of CO poisoning [31].

4.1 Laboratory Investigations:

This study revealed that only a quarter of patients was hypoxic, as they were reported to receive oxygen therapy before referral to the poison center, whereas most patients had metabolic acidosis as acute CO poisoning results in decreasing the oxygen-carrying capacity of blood and delivery of oxygen to tissues, and hence lactic acidosis [32]. This is consistent with the results of Barghash et al. (2017) [33]. Abnormally high troponin levels were detected in 70% of patients in this study, reflecting myocardial injury due to generalized hypoxia and the direct toxic effect of CO on the heart [34].

This study revealed that COHb was abnormally high in most patients and related significantly with clinical manifestations. This is in line with Hullin et al. (2017) [35]. In this study, normal ranges of COHb levels were recorded among 3.3% of patients, which may be explained by the late presentation in these cases, making the process of diagnosing acute CO poisoning more difficult and provoking the need for novel biomarkers to reach a proper diagnosis**.**

4.2 Neutrophil Lymphocyte Ratio (NLR)

Most studied patients showed high neutrophil counts, reflecting inflammation, in agreement with Moon et al. (2019) [36], whereas the recorded low lymphocyte counts reflected poor general condition and increased physiological stress [37]. A CO poisoning mechanism is that it activates nitric oxide and other oxygen free radicals generated by xanthine oxidase [38]. Xanthine oxidase is produced in situ from xanthine dehydrogenase via enzymes released by leukocytes that adhere to damaged endothelial cells due to reperfusion injury occurring during recovery from CO intoxication [8, 39].

NLR in this work was abnormally high in most patients and related significantly with COHb and IMA, which is consistent with Prockop and Chichkova (2007) [40] Moreover, Karabacak et al. (2015) [41] showed a significant elevation of NLR in acute CO poisoned patients, but did not relate significantly with COHb level.

This study showed a significant relation between NLR and initial neurological manifestations (GCS, CT brain), which may be due to a significant increase in leukocyte sequestration in the brain microvasculature following exposure to CO poisoning [42]. It was recorded that CO causes activation of N-methyl-D-aspartate neurons in the brain, with subsequent over-activity of neuronal nitric oxide synthase causing perivascular changes that cause neutrophil sequestration or activation [43].

4.3 Ischemia Modified Albumin (IMA)

In this study, IMA was measured to determine its role in the diagnosis and assessment of clinical severity and its relation to delayed neurological manifestations. It showed a highly significant increase in CO-intoxicated patients compared with the control group, as tissue hypoxia due to CO poisoning potentiates vascular permeability and causes increased accumulation of interstitial fluid with decreased circulating blood volume and ischemia affecting multiple organs [44]. Tissue hypoxia, ischemia, and oxidative stress related to CO poisoning may alter the N-terminus of human serum albumin, resulting in IMA formation within minutes of the onset of ischemia, with a peak lasting for 6–12 h [45]. These findings reflect the study of Baydin et al. (2016) [46], who noticed significantly higher IMA levels in acutely CO-intoxicated patients.

Furthermore, this research study showed that IMA related significantly with initial neurological manifestations (GCS, CT brain) and COHb, in contrast to Turedi et al. (2011) [47], who recorded insignificant relationships between COHb and IMA levels [47]. This may be attributed to variable COHb levels in this study compared to that of Turedi et al. (2011) [47].

4.4 Delayed Neurological Sequelae:

The diagnosis of DNS in this study relied upon neuropsychometric testing of cognitive abnormalities (MMSE) and abnormal brain MRI findings conducted six months after acute intoxication. This study revealed that more than a quarter of patients developed DNS, which was slightly higher than that previously reported by Pepe et al. (2011) [10] and Kuroda et al. (2015) [8], but lower than previously reported by Weaver (2009) [48] and Mohammed et al. (2016) [49]. DNS among patients in this study could be attributed to CO-induced hypoxia in the acute event followed by reoxygenation injury to the brain leading to increased production of ROS, which could oxidize essential proteins and nucleic acids and produce brain lipid peroxidation [50].

In this study, more than one third of cognitively impaired patients, evidenced by low MMSE scores, showed abnormal hyperintense signals in white matter and globus pallidus in T2-W and flair sequences of MRI brain imaging conducted six months after acute intoxication. This agrees with that of Weaver et al. (2015) [51] and Nah et al. (2020) [9], who reported the same findings in brain MRI.

Selective affection of globus pallidus by CO intoxication was reported and attributed to hypotensive effects of CO on these structures with poor anastomotic vascular supply, or a direct binding of CO to the heme iron in globus pallidus, a region of the brain with the highest iron content [52], whereas, white matter hyperintensities were thought to result from delayed post hypoxic demyelination that was caused by biochemical changes triggered by accumulation of metabolic byproducts [53]. Furthermore, Lin et al. (2009) [30] stated that microstructural white matter pathology in CO intoxication was related to delayed cognitive encephalopathy.

It is also noteworthy that, a longer duration of exposure related significantly with DNS in this study due to prolonged tissue hypoxia, as CO exposure could lead to drowsiness and muscle weakness, making escape from the site of exposure difficult [54]. This was in agreement with Helal et al. (2019) [55]. Moreover, there were insignificant differences between DNS and non-DNS groups with respect to age, indicating that the risk of DNS was present in all age groups.

Significantly lower initial GCS scores were recorded among patients, who developed DNS in this work, as CO-induced tissue hypoxia leads to loss of consciousness and reoxygenation injury to the central nervous system [56]. This is consistent with the results of Chan et al. (2016) [57] and Zhang et al. (2021) [58].

Moreover, patients with abnormal brain imaging (CT brain) were significantly higher in DNS group than in non-DNS group, in accordance with Liao et al. (2018) [59]. Furthermore, other reports have identified an association between brain imaging abnormalities presenting in the basal ganglion or cerebral white matter regions and DNS development [28, 60].

Regarding the cardiovascular effects of CO poisoning, blood pressure was significantly lower in DNS group than in non-DNS group. This finding is in line with Pepe et al. (2011) [10], who stated that SBP of ≤90 mmHg was considered a risk factor for DNS development. Moreover, troponin levels were significantly higher in DNS group than in non-DNS group due to more prolonged exposure to CO-induced hypoxia, evidenced by significantly lower SaO2 in DNS group. This was in accordance with Kuroda et al. (2015) [8], while Gaballah et al. (2020) [61] revealed insignificant differences between the two groups regarding oxygen saturation, which can be explained by pre-admission oxygen therapy or different assessment time.

In this work, a statistically significant increase in COHb level was identified in DNS group compared to non-DNS group in accordance with Gaballah et al. (2020) [61]. Conversely, Guan et al. (2015) [62] concluded that COHb concentration was an insignificant predictor of DNS development. This variation may be related to factors, such as duration of exposure to CO, time of withdrawing blood samples, and efficiency of oxygen administration.

In this study, NLR was significantly higher in DNS patients, which can be explained by the fact that neutrophils are potential biomarkers for inflammation as their activation promotes the synthesis of inflammatory cytokines [63].

Conversely, lymphopenia reflects an increase in the release of catecholamines and corticosteroids, both of which increase pro-inflammatory cytokine levels [64]. This was supported by Thom et al. (2006) [12], who reported the association between inflammation and neurological Sequelae after CO poisoning.

The novel biomarker, IMA, showed a highly significant elevation in DNS relative to non-DNS group. This could be ascribed to the fact that its level rises in response to various hypoxic and ischemic conditions, oxidative stress, and acidosis [65]. Additionally, the association between IMA and hypoxic brain injury has been reported. It was found that the surface of the brain cells is rich in unsaturated fatty acids, causing the brain to be susceptible to ischemia and hypoxia in brain cells [66]. It has been demonstrated that ROS can increase serum IMA levels within minutes, with the aggravation of cerebral tissue ischemia and hypoxia, increasing and accumulating lactic acid, which also promotes IMA production [67].

This study showed that the DNS group required HBO significantly more than non-DNS group, which could be explained by the fact that those patients initially presented with neurological manifestations. This was in tune with Fujita et al. (2021) [68], who concluded that the need for HBO sessions was associated with a higher incidence of DNS, as it may already be too late to reduce or alleviate damage to the central nervous system if HBO therapy was delayed.

According to univariate analysis, this study revealed that the initial presenting clinical variables, which could predict the development of DNS after acute CO poisoning included prolonged duration of exposure to CO, increased time passed since exposure, low GCS, hypotension, abnormal CT brain findings, and the need for HBO therapy. Additionally, laboratory variables on admission associated with the development of CO-related DNS included elevated COHb level, decreased oxygen saturation, low HCO3, as well as high IMA and NLR.

Analysis of ROC curves of IMA and NLR levels on admission suggested that they could be useful biomarkers for predicting the risk of development of DNS among the studied patients. Moreover, this study concluded that >95 µg/ml IMA and >5.67 NLR can predict DNS development in acute CO-intoxicated patients.

CONCLUSION

The studied markers (NLR and IMA) on admission could be employed as useful biomarkers for correlation with acute CO poisoning severity and predicting the acute CO poisoning outcome including development of DNS or not.

Recommendations:

Proper clinical and laboratory evaluation of any suspected case of acute CO poisoning should be performed, especially for parameters proved to be predictors of DNS, including NLR and IMA. Additionally, follow-up of cases using neuropsychiatric testing should continue for early DNS detection.

Statements and Declarations:

Availability of data and materials: The authors confirm that the data supporting the findings of this study are available within the article and/ or its supplementary materials.

Author Contributions

Maha Ghanem and Safaa Elshanawany participated in the design of the study, data interpretation, and critical revision of the manuscript and its final version. Mona Ashry participated in the design of the study and performed the data analysis. Aya Abdelgaleel participated in analysis and interpretation of radiological data. Nehad Gad participated in the design of the study, data collection, and drafting the manuscript. Wael Kholeif participated in data interpretation and reviewing the manuscript and its final version.

Ethics Approval and Consent to Participate:

Approval was obtained from the Research Ethics Committee of Faculty of Medicine, Alexandria University (IRB Number: 00012089, FWA Number: 00018699, Approval serial number: 0201435).

Conflict of interest: None to be declared.

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